IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application	Confirmation No.: 5176
Inventors: Jonathan W. Nyce	Art Unit: 1617
Application No.: 10/072,010	Examiner: Jiang, Shaojia A.
Filed: October 25, 2001	
Title: Compositions, Formulations and Methods for Prevention and Treatment of Diseases and Conditions Associated with Bronchoconstriction, Allergy(ies) and Inflammation	Customer No. 021971

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION PURSUANT TO 37 CFR §1.132

Sir/Madam:

I, Dr. Cynthia B. Robinson, M.D., do hereby declare as follows:

1. I am Vice President of Clinical Development at Epigenesis Pharmaceutical, LLC (New Jersey, NJ, USA). I received my M.D. from Jefferson Medical College (Philadelphia, PA, USA) in 1982. I have over six years of experience in drug development and have been working in the area of pulmonary/critical care since 1989, which encompasses the treatment of asthma and other pulmonary diseases and disorders. My Curriculum Vitae is attached as Appendix A.

2. I am familiar with the prosecution history of the above-identified patent application and the pending office action dated December 14, 2004. I am aware of the rejection of the claims in this pending office action under 35 USC §112 and §103.

3. I am submitting this declaration to show that the a composition of dehydroepiandrosterone (DHEA) or its pharmaceutically acceptable salts in a respirable composition with particles in the respirable size range is not anticipated or obvious over the prior art.

The references cited by the Examiner, Remington and Lieberman, describe a nasal inhalation formulation, which will not effectively dose the lung nor treat pulmonary conditions. Formulations

optimized for topical nasal instillation contain particles that are unsuitable for deeper lung penetration. Aerosol formulations that can dose the lung are thus distinct from nasal formulations.

In our hands, use of respirable dehydroepiandrosterone-sulfate (DHEA-S) produces the unexpected results of low systemic absorption without systemic effects as observed in the toxicology studies described below. I include below one animal study and two human studies, which demonstrate the efficacy of, inhaled DHEA-S in treating asthma, while producing minimal systemic side-effects. The particle size of the DHEA-S in the formulations used in these studies was about 1 μm to about 5 μm. All these experiments were performed under my supervision.

4. The lungs receive a quarter of the cardiac output every minute, and the lung is separated from the blood stream by about one cell diameter at the alveolar level. Therefore, the lung has a massive surface area that can be used to dose the systemic circulation. However, in the three studies described below, only a modest increase in circulating DHEA-S was observed. Furthermore, the minimal increase in circulating levels produced minimal adverse effects on humans and animals, thus being counterintuitive that lung dosing produces systemic exposure.

5. In an animal study we investigated the potential toxicity and toxicokinetics of DHEA-S during daily inhalation administration to dogs for 13 consecutive weeks followed by a 4-week recovery period.

The study design is depicted in TABLE 1:

TABLE 1

Group No. Identification	Target Inhalation (mg/kg/day)	Number of Animals			
		Main Study		Recovery	
		Males	Females	Males	Females
1 Lactose Control	0	4	4	2	2
2 DHEA-S – Low Dose	0.25	4	4	-	-
3 DHEA-S – Mid Dose	1.00	4	4	-	-
4 DHEA-S – High Dose	4.00	4	4	2	2

All animals were examined twice daily for mortality and signs of ill health. Detailed examinations were performed at least once prior to treatment, weekly during the treatment and

recovery periods. Individual body weights were recorded on the day of randomization, and weekly through the treatment and recovery periods, and on the day of necropsy. Individual food consumption was recorded daily starting 2 weeks prior to dosing and extended through the treatment and recovery periods. Respiratory minute volume was assessed twice pretreatment. Electrocardiograms were evaluated once pretreatment and on Week 13. Laboratory investigations (hematology, clinical biochemistry and urinalysis) were performed once pretreatment (all animals) and at termination of the treatment and recovery periods. Ophthalmologic evaluations were performed pretreatment and at Week 13 of the treatment period. Toxicokinetic assessments were performed on Days 1 and 90 for DHEA and DHEA-S determination. At termination, selected organs were weighed and a gross pathological examination was performed, selected tissues were retained and processed for histopathological examination, and examined.

The achieved dose of DHEA-S in the lungs is shown in TABLE 2:

TABLE 2

Group	Gender	RMV (L/min)	Action conc'n (mg/L)[a]	Exposure duration (min)	MMAD (µM)[a]	Pulmonary Deposition Fraction	Body weight (kg)	Pulmonary Calculated Achieved Dose (mg/kg/day)
2 DHEA-S Low-Dose	Male Female	4.91 3.97	0.051	15	2.6	0.75	11.38 9.80	0.248 0.232 0.240[b]
3 DHEA-S Mid Dose	Male Female	4.08 3.31	0.194	20	2.8	0.76	11.49 9.16	1.05 1.07 1.06[b]
4 DHEA-S High Dose	Male Female	4.91 3.41	0.555	20[d]	3.0	0.76	11.34 9.38	3.65 3.07 3.36[b]
4 DHEA-S High Dose	Male Female	4.91 3.41	0.558	25[e]	2.9	0.76	11.94 9.86	4.36 3.67 4.02[b]
4 DHEA-S High Dose Overall[f]	Male Female	4.91 3.41						3.84 3.23 3.54[b]

a Based on analytical results
b Mean of males and females
c Mean of body weight occasions during the treatment period
d Group 4 animals were exposed for 20 minutes from Days 1 to 68 (chamber concentrations, MMAD and body weights from Weeks 1 to 10 are used for calculations).
e Group 4 animals were exposed for 25 minutes from Days 69 onwards (chamber concentrations, MMAD and body weights from Weeks 11 to 13 are used for calculations).
f Group 4 overall achieved doses is calculated as 68 days of the first dose and 24 days of the second dose, reported on a daily basis.
RMV – respiratory minute volume
MMAD – Mass median aerodynamic diameter

TABLE 3 shows a summary of the systemic levels of DHEA and DHEA-S.

TABLE 3

Group	Occasion	DHEA-S		DHEA	
		Mean C_{max} (ng/mL)	Mean $AUC_{0\text{-tlast}}$ (ng*h/mL)	Mean C_{max} (ng/mL)	Mean $AUC_{0\text{-tlast}}$ (ng*h/mL)
2 Males	Day 1	44.3	73.0	8.62	72.3
	Day 90	55.2	133	3.53	52.4
2 Females	Day 1	86.0	153	1.37	10.6
	Day 90	121	331	1.54	17.6
3 Males	Day 1	306	605	7.04	40.2
	Day 90	311	574	6.33	74.6
3 Females	Day 1	334	619	3.73	15.1
	Day 90	299	799	3.43	22.9
4 Males	Day 1	862	1775	12.5	75.1
	Day 90	726	2241	10.6	94.8
4 Females	Day 1	675	1578	10.2	40.3
	Day 90	1007	3133	7.67	52.0

No treatment-related mortality or clinical signs of side-effects were seen during the treatment or recovery periods. Slightly lower body weights were noted in Groups 2 and 4 males and in Groups 3 and 4 females during the treatment phase. Slightly lower food consumption was noted in Groups 3 and 4 females during the treatment phase. Electrocardiography, ophthalmology, hematology, serum chemistry and urinalysis parameters were considered unaffected by the test article. There were no compound-related organ weight, microscopic or macroscopic changes that could be attributed to DHEA-S.

Both the C_{max} and AUC values of DHEA-S generally displayed dose response relationships on both sampling occasions, with little to no overlapping between dose groups. DHEA analysis revealed no obvious relationship between C_{max} and dose with observed peak concentrations generally occurring 1 hour post dose. C_{max} and AUC values showed only slight increasing trends with increasing dose levels. Exposure to DHEA-S generally increased on Day 90 when compared to Day 1, after accounting for the different dose levels administered on Day 1 and 90 for Group 4. Inter-individual variability in exposure, however, was high and some overlapping did exist. Exposure to DHEA, however, did not show any consistent sign of accumulation after repeated dosing.

In conclusion, inhalation exposure of dogs to DHEA-S for 13 weeks, at dosages up to 3.54 mg/kg/day was well tolerated and produced no treatment-related clinical signs or changes in electrocardiogram, ophthalmology, hemograms, serum biochemistry and urinalysis parameters. Slight decreases in body weights and food consumption were noted during the treatment period. There were no changes in organ weights, macroscopic and microscopic evaluation. Based on slight changes in body weight observed, the highest dose of 3.54 mg/kg/day, which is about 90 times more than our current highest dose administered to human lungs, was considered to be the no observed adverse effect level. Increases in hematocrit, glucose and muscle mass would be expected if a significant systemic effect was observed. Furthermore, changes in pituitary, adrenal glands and sex organs would be expected if a systemic effect was produced by aerosol administration.

6. Similarly, in a human study, inhaled DHEA-S produced minimal systemic side-effects.

A study was also performed to study the safety, tolerability and multiple dose pharmacokinetics of inhaled dry powder DHEA-S in healthy elderly volunteers, 45 and older. Effects on markers of bone turnover were measured and compared with inhaled budesonide.

This was a randomized repeat-dose, single-blind, placebo-controlled, dose-ascending safety, tolerability and PK study of DHEA-S (once daily) with parallel groups receiving placebo and inhaled budesonide (twice daily) for 13 days in a healthy elderly population. There were four study cohorts each of 10 subjects randomized to DHEA-S, its placebo, or budesonide in a 6:2:2 ratio. The 4 cohorts differed only with respect to the ascending dose of DHEA-S and a corresponding number of inhaler placebo capsules. Two actuations of Budesonide were given twice daily using the Pulmicort Turbuhaler®, which delivers 200 µg per actuation or 800 µg total daily dose. There was a comparison of changes in bone turnover markers in each active group versus placebo.

On day 1, a control serum profile of DHEA-S/DHEA was obtained from subjects during a 24-hour overnight stay. On day 1, they were given a first dose of inhaled DHEA-S, placebo or budesonide and remained in the clinic for another 24-hour stay to have a PK profile of DHEA-S/DHEA and serial FEV1 determinations performed. On day 2, subjects had a single predose PK determination, spirometry, and safety assessment obtained. From days 3-6, subjects dosed at home. On day 7 they returned to the study center for an interim safety check. Subjects continued treatment through day 13. Subjects returned on day 13 for a bone marker profile and a PK profile. Subjects

remained overnight in the clinic until day 14 to complete the bone marker profiles, morning PK and for safety assessments. Subjects returned on day 15 for 48-hour bone marker profiles, morning PK and for safety assessments. On day 28, subjects returned for a safety follow-up final visit.

Each DHEA-S capsule contained 25 mg of material (DHEA-S plus lactose), which includes 6.25 mg of active DHEA-S drug substance of which ~1.7 mg is in the respirable range. So, 10 capsules would deliver a maximum of approximately 17 mg of active ingredient to the lung. The number of DHEA-S capsules per cohort was 1, 2, 5 and 10. Table 4 depicts the dosing summary.

TABLE 4

Groups	DHEA-S		Placebo		Budesonide	
	# subjects	#capsules/day	#subjects	#capsules/day	# subjects	Dose/day
cohort 1	6	1	2	1	2	800 µg
cohort 2	6	2	2	2	2	800 µg
cohort 3	6	5	2	5	2	800 µg
cohort 4	6	10	2	10	2	800 µg

40 normal elderly volunteers were studied. All subjects completed dosing as scheduled and there were no drop-outs or withdrawals. There were no serious adverse events. Non-serious adverse events are summarized below in TABLE 5.

TABLE 5

	# of Capsules per day	Adverse Events (Likely, probably or possibly related only) (DHEA-S TREATED ONLY)
Cohort 1	1	NONE
Cohort 2	2	• Bitter taste in mouth after dosing • Tired
Cohort 3	5	• Blister on lip • Headache • Stomach ache • Tired
Cohort 4	10	• Globus Syndrome (feeling of something stuck in throat)

Pulmonary function data remained normal throughout the study, including immediately after dosing 10 capsules. No safety laboratory values of potential clinical concern were reported in ECGs,

hemograms, or clinical chemistry. There was a dose related increase in serum exposure to DHEA-S but not to DHEA, the first metabolite of DHEA-S. However, this modest increase in serum DHEA-S levels was unaccompanied by increases in circulating sex hormones.

TABLE 6 has the summary of circulating levels of DHEA-S exposure after 13 days of repeat dosing. One patient in the 10 capsule group had two values in a 24 hour profile that were greater than 5600 ng/mL value, however, this patient's average value was well within the normal range. All values from all other patients were in the normal range. DHEA (the first metabolite of DHEAS) levels remained constant. So, an increase in circulating levels of DHEA was not observed.

TABLE 6

	Placebo	1 cap	2 Cap	5 Cap	10 Cap	Normal Range
DHEA-S ng/mL mean (range)	1551 (388-2966)	**1152 (700-2442)**	1714 (1321-2083)	3963 (3377-4671)	4837 (3531-6100)	700-5600
DHEA ng/mL mean (range)	3.1 (0.8-7.4)	1.9 (1.1-2.9)	3.1 (2.2-4.1)	3.4 (2.7-4.4)	5.0 (3.6-6.5)	1.4-12.5

The effect of 13 days of DHEA-S administration on cortisol responses and on sex hormone levels was also examined. DHEA-S is a C_{19} adrenal steroid and it can be metabolized to testosterone or estradiol. As shown in Table 7, the levels of testosterone and estradiol were unchanged, as any changes were within the normal day-to-day assay variability. For estradiol, the functional sensitivity of the estradiol assay (i.e. the lowest level at which the CV of the assay is 20%) is 15 pg/mL. Many of the subjects had estradiol levels lower than this. Therefore, while mean estradiol levels on day 13 in the 10CAP group might appear higher than baseline, the difference of only ~ 7 pg/mL is not clinically meaningful as differences of this magnitude could also be seen with repeated measures of the same sample. The data suggest that there is no dose-response relationship between the active drug and testosterone or sex hormone binding globulin (SHBG).

Table 7 shows the mean 24 hour concentrations of sex hormones at baseline and at the end of dosing by group. Note only women had estradiol measured and only men had testosterone measured. Both genders had SHBG determinations. Table 8 contains the normal ranges.

TABLE 7

	Estradiol pg/mL		Testosterone ng/dL		SHBG nmol/L	
	Day –1	Day 13	Day –1	Day 13	Day –1	Day 13
Placebo	10.8	9.8	509.3	527	56.7	56.5
1 capsule	8.7	8.3	370	381	42.8	37
2 capsules	13	14.2	N/A	N/A	58.2	55
5 capsules	11	15	344.3	388.8	32.2	31.5
10 capsules	10.8	16.5	403	399	47.2	41

TABLE 8

	Normal Ranges
Estradiol	0-49 pg/mL – F
Testosterone	303-995 ng/dL – M
SHBG	10-55 M; 11-75 nmol/L – F

When DHEA is administered via the systemic route, a decrease in cortisol levels is observed, see Adebowale, Ph. D., Office of Clinical Pharmacology and Biopharmaceutics, Results of adrenal function testing with Cortrosyn® (synthetic ACTH) stimulation following dosing of GL701 at a dose of 200 mg once daily for 28 days. However, following inhalation of DHEA-S, no such decrease in cortisol was observed on either baseline levels or post-ACTH stimulation levels after 13 days of dosing of DHEA-S at 1, 2, 5, or 10 capsules/day.

In summary, 40 normal elderly volunteers were dosed with DHEA-S, placebo, or budesonide in this safety study. Although increases in DHEAS C_{max} and AUC above baseline levels were observed, there were no adverse effects on pulmonary function, cortisol levels, sex hormones or clinical laboratory parameters of potential clinical concern.

7. A second human study demonstrated the efficacy of respirable DHEA-S in the treatment of asthma with minimal systemic side effects. The results of this study were published in abstract form, which is attached as Appendix B.

This human study investigated whether repeated inhalation of DHEA-S, a nonglucocorticoid steroid in an aqueous aerosol solution, reduces the early-phase (EAR), late-phase (LAR) reactions and bronchial hyperresponsiveness after allergen challenge in patients with mild allergic asthma.

The study was a double blind, placebo controlled, randomized crossover trial. Patients underwent a methacholine (MCh) challenge, a dose-ascending allergen challenge, and a single dose

allergen challenge during the screening period. Patients were randomized to one of 2 treatment sequences (DHEA-S/placebo or placebo/DHEA-S). Each treatment period lasted for 5 days with a minimum 3 week washout between sequences. Patients received 25 mg DHEA-S or placebo once daily with the Pari® nebulizer. On days 4 and 6, patients had bronchial MCh hyperresponsiveness determined. On day 5, patients were subjected to a single dose allergen challenge. 24 asthmatic patients (mean forced expiratory volume in one second (FEV1) of 96.5% predicted) who experienced an EAR and LAR after allergen challenge (prescreened) participated in the study.

Inclusion Criteria:

- Mild asthma with FEV1 at the time of screening >70% predicted.
- *Late* asthmatic response = max fall FEV1 ≥ 15% between 3 - 8 hrs in dose-ascending allergen challenge
- *Early* asthmatic response = max fall FEV1 ≥ 25% between 0 - 2 hrs in dose-ascending allergen challenge
- *Late* asthmatic response = max fall FEV1 ≥ 15% and an additional time point with a max fall FEV1 ≥ 10% between 3- 8 hrs after single dose allergen challenge

Results: Treatment with placebo resulted in a mean maximal drop in FEV1 from hours 0-2 (EAR) of –29.7% ± 2.5 (mean, SEM) and -20.2% ± 2.2 (mean, SEM) fall in FEV1 3-8 hours (LAR). Following treatment with DHEA-S, there was a significant ($P<0.05$) attenuation in LAR compared to the corresponding placebo treatment arm; -13.5% vs –20.2%. The LAR AUC for FEV1 was also attenuated (-0.91% vs.-1.73%, $P< 0.01$). There was a trend toward improvement in bronchial hyperresponsiveness following treatment with DHEA-S. There was no significant effect on EAR (-27.1 % vs. –29.7 %).

Table 9 contains the demographic data of the participants in this study.

TABLE 9

CHARACTERISTIC	MEAN	(RANGE)
Age, (yr)	32	20-45
FEV1, (L)	4.36	3.7-5.4
FEV1, (% pred.)	96.5	74-122
FEV1/FVC	76.3%	59-97
PC20 mg/mL (geometric mean)	0.78	0.05-7.54
Allergen type (%)		
Grass 46	Dust 25	Cat 13

Safety: Five days of daily dosing of DHEA-S was safe and well-tolerated in mild asthmatics. Diary cards were kept and reviewed every day. Safety laboratory data was collected and tabulated. No serious adverse events, no withdrawals due to lack of effect/exacerbations, and no laboratory values of potential clinical concern were observed. Also, no effect on androgenic parameters was observed. 24 hour average concentration of testosterone with DHEA-S was 572 ± 191 ng/mL and with placebo was 593 ± 214 ng/mL. 24 hr average concentration sex hormone binding globulin (SHBG) with DHEA-S was 30.3 ± 10.7 ng/mL and with placebo was 32 ± 12 ng/mL.

The effect of five days dosing with DHEA-S was studied on the late asthmatic response (max fall in FEV1 and AUC 3-8 hrs), bronchial hyperresponsiveness and symptoms. Figure 1 shows that challenge with allergen led to the anticipated early and late response.

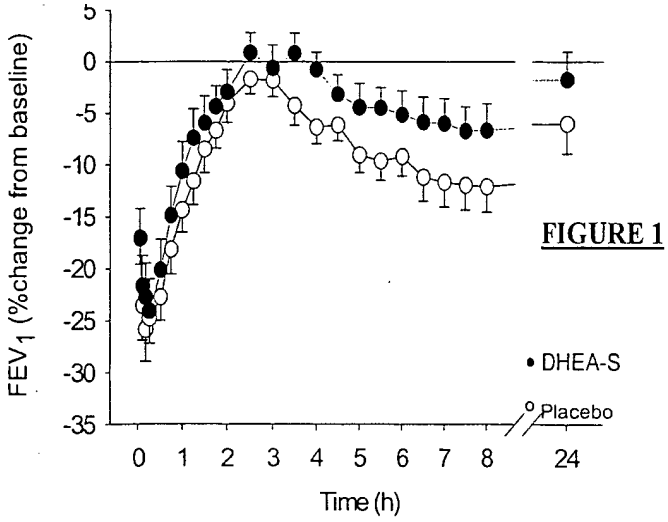

FIGURE 1

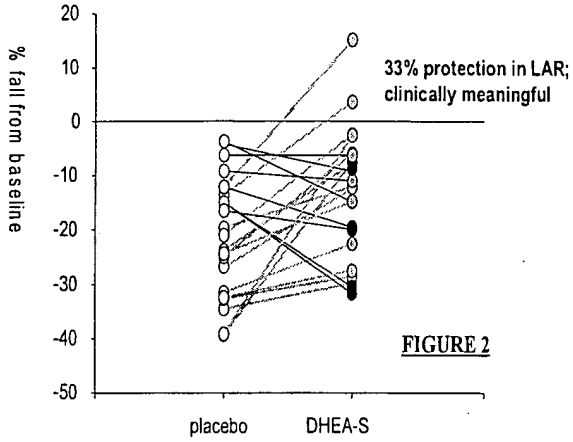

FIGURE 2

Figure 2 depicts the maximum fall in FEV1, LAR. Per patient analysis of effect of allergen challenge after 5 days of treatment with either placebo or 25 mg of DHEA-S is shown in Figure 2. DHEA-S significantly ($p < 0.05$) attenuated the maximal fall in FEV1 in the LAR compared to placebo -13.5 ± 2.4% vs –20.2 ± 2.2%.

FIGURE 3

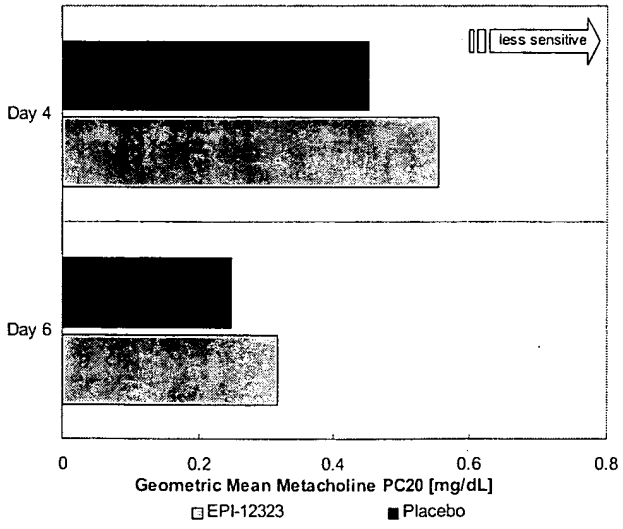

Figure 3 depicts changes in PC20 MCh. PC20 measures the amount of methacholine required to produce a 20% drop in pulmonary function. An improvement trend was observed in hyperresponsiveness after allergen challenge. A significant period effect was noted in day 4 results favoring DHEA-S, suggesting that a drug carryover effect may be responsible (analysis not shown).

TABLE 10

	Total Symptom Score				
	Cough	Chest tightness	SOB (short breath)	Wheeze	TOTAL
DHEA-S	16	29	20	17	82
Placebo	27	41	32	22	122

Table 10 contains the results from diary cards for cardinal asthma symptoms that were tabulated every day. Symptoms were weighted, summed daily and compared between groups. Table 10 contains total symptoms recorded after 5 days of dosing with either placebo or DHEAS.

Conclusions: Five days of once daily administration of DHEA-S significantly attenuated the LAR, reduced bronchial hyperresponsiveness in these mild asthmatics. The magnitude of protection against allergen challenge is clinically relevant. DHEA-S was well tolerated and reduced asthmatic symptoms, reduced nocturnal awakenings, and reduced rescue beta agonist use.

8. Overall, all three studies demonstrate that inhalation of small particle size DHEA-S produces minimal systemic side effects. This is an unexpected result as it would be expected that the greater access to the systemic circulation in the lungs would cause systemic absorption and result in systemic side-effects such as modified levels of sex hormones and/or adverse effects on the sex organs. Unexpectedly, minimal systemic side effects were observed and a beneficial effect on asthma was observed.

9. I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that making of willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful statements may jeopardize the validity of the applications or any patent issuing thereon.

Respectfully submitted,

Dated: March 10, 2005

Cynthia B. Robinson, M.D.
Vice President of Clinical Development
Epigenesis Pharmaceuticals, LLC

APPENDIX A

CURRICULUM VITAE

CYNTHIA BROUSE ROBINSON
MD

6 Jan 2005

CURRICULUM VITAE

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A DATE: 28-Jan-2005

B BIOGRAPHICAL INFORMATION

BIRTHPLACE: Washington, DC

CITIZENSHIP: USA

MARITAL STATUS: Married, David M. Robinson, MD

CHILDREN:

Kelly Christine	4/17/85
Matthew Karl	12/17/88

PRESENT TITLE: VP, Clinical Development, Epigenesis Pharmaceuticals

C CAREER OBJECTIVES

Long-term:

- Manage and provide strategic focus for a clinical group responsible for development of a balanced portfolio, including marketed products and early phase compounds, preferably in pulmonary. Direct multidisciplinary team to submit and gain approval of NDAs, sNDAs.

Near term:

- Direct and develop a multidisciplinary development team to progress compounds from target validation through to, including clinical proof-of-concept in respiratory disease. Acquire understanding of biotechnology business aspects and deliverables. Immersion into strategic business development to add value to the company. Expand

experience in CMC, toxicology and regulatory affairs for pulmonary products. Acquire additional experience in pivotal trial conduct. Acquire additional experience in deriving target product profiles and developing and implementing clinical development plans to realize key TPP elements and maximize their value. Participate in multidisciplinary team engaged in evaluating in-licensing opportunities.

D INDUSTRY EXPERIENCE:

1/02-current
VP, Clinical Development, Epigenesis Pharmaceuticals
Responsible for all preclinical and clinical development of respiratory compounds including small molecules and inhaled oligonucleotide compounds (NME). Responsible for supervising regulatory affairs, CMC, quality assurance and clinical development. Responsible for supervision of CRO support including data management, biostatistics, manufacturing, packaging, toxicology, clinical study support. Responsible for integration of discovery and development objectives. Supervision of 3 direct reports. Chief medical officer. Responsible for clinical development of EPI 2010 (phase II asthma), EPI 12323 (phase IIa asthma and COPD) including TPP, development plans and clinical study design. Successful completion of 7 clinical trials including 2 POC studies and support of 2 IND applications. Successful completion of 6 preclinical toxicology studies and oversight of 2 dry powder formulation developments.

2/01-1/02
Director, Clinical Drug Discovery, Respiratory, Inflammation, Respiratory Pathogens, CEDD
Responsible for early clinical development (candidate selection through IIa) of pulmonary and rheumatoid arthritis compounds with a major focus on COPD including:

development of TPP for RA and COPD indications
development of asset product profiles for 9 early compounds in portfolio
development of early clinical development plans
development of clinical protocols to support early development
recruit/train/supervise of physicians/scientists
development of mechanism of action protocols using novel/surrogate endpoints in COPD and RA
preparation of strategic disease area review documents
preparation of regulatory reports
maintenance of budgets/contracts for CEDD-sponsored studies

8/99-2/01
Director, Pulmonary/Diabetes Clinical Research and Medical Affairs
SmithKline Beecham Pharmaceuticals

Responsible for clinical development (phase II and III) of pulmonary compounds including :

- development of clinical plans to fit TPP
- conduct of large phase III studies (study operations, budgeting, monitoring, medical oversight)
- preparation of reports and regulatory documents (oversight of data handling, data interpretation, IB, ISS)
- leadership of matrix functional teams including chair of clinical working groups
- medical affairs support by participation in publication review. Experience with commercial-clinical interface and KOL development.
- extensive experience with discovery-clinical interface by providing input to early development strategy including Go/No Go decision points, appropriate experimental models, extrapolation of animal data to patient treatment settings
- supervisory role to clinical research scientists
- Member of the following teams:1) US Med Director IL-5 Mab, 2) Cilomilast (Ariflo) asthma program, 3) Cilomilast mechanism of action studies, 4) Cilomilast CR COPD program (shared responsibility) 5) p38 MAP kinase inhibitor program (pulmonary indications), IL-8 receptor antagonist (pulmonary indications)

7/97-8/99
Director, Clinical Pharmacology SmithKline Beecham Pharmaceuticals
Responsible for early clinical development (phase I) and experimental medicine of lead and back-up compounds in a variety of therapeutic areas including:

- preparation of early clinical development plans including experimental studies and proof-of-compound activity studies
- preparation of reports, (32) protocols (15) and regulatory documents (INDs, IND updates)
- conduct of phase I studies including first-into-man protocols
- extensive interface with IRB and instruction /education about good clinical practice
- provision of pulmonary expertise for in-licensing opportunities, due diligence provided on safety and efficacy for antihistamine compound
- supervision and medical director of Clinical Laboratory (two direct reports, 50 indirect reports)
- supervision and mentorship of Assist. Director, H. Chou, M D, PhD
- Responsible compounds: IL-4 Mab, NK3 receptor antagonists (lead and back-up compounds), Osteoclast vitronectin receptor antagonists, including development of experimental medicine model of accelerated bone resorption model (lead and back up), Ornade/Lithium spansules, endothelin receptor antagonists (IV and oral formulations) including MOA study.

E EDUCATION:

9/72 - 10/76	B.S.	Northwestern University, Evanston, IL (Physical Therapy)
9/78 - 6/82	M.D.	Jefferson Medical College, Philadelphia, PA

F POSTGRADUATE TRAINING AND FELLOWSHIP APPOINTMENTS:

7/82 - 6/85	Internship and Residency, Department of Internal Medicine, University of Pennsylvania School of Medicine, Philadelphia, PA
7/85 - 6/88	Fellowship, Cardiovascular/Pulmonary Division, Department of Internal Medicine, University of Pennsylvania School of Medicine, Philadelphia, PA
7/88 - 6/90	Fellowship, Division of Pulmonary and Critical Care Medicine, University of California, Davis, Medical Center, Sacramento, CA

G FACULTY APPOINTMENTS:

7/90 - 3/94	Assistant Professor in Residence, Division of Pulmonary and Critical Care Medicine, University of California, Davis, School of Medicine, Sacramento, CA
3/94 – 7/97	Assistant Professor of Medicine, Pulmonary and Critical Care Division, Department of Internal Medicine, University of Pennsylvania School of Medicine, Philadelphia, PA
7/97- 2003	Assistant Adj. Professor of Medicine, Pulmonary and Critical Care Division, Department of Internal Medicine, University of Pennsylvania School of Medicine, Philadelphia, PA
7/2003-present	Assoc Adj. Professor of Medicine, Pulmonary and Critical Care Division, Department of Internal Medicine, University of Pennsylvania School of Medicine, Philadelphia, PA

H SPECIALTY CERTIFICATIONS:

1983	National Board of Medical Examiners

1985	American Board of Internal Medicine
1988	Subspecialty Certification in Pulmonary Medicine
1989	Subspecialty Certification in Critical Care Medicine
1999	Renewal Certification in Critical Care Medicine

I **PRINCIPAL INVESTIGATOR OF GRANTS:**

"Regulation of Fibronectin mRNA by TGFb." University of California, Davis — Young Investigator's Award, American Lung Association of California, $19,000. 7/1/90-6/30/91.

"Regulation of Fibronectin mRNA by TGFb." University of California, Davis — Francis B. Parker Fellowship Award, $96,000. 8/1/90-7/31/93.

"TGFb and TGFa Gene Expression by Cigarette Smoke." University of California, Davis — California Tobacco-Related Disease Research, $75,000/year. 7/1/90-6/30/93.

"The Role of Fibronectin in Tracheal Epithelial Cells." University of California, Davis — Young Investigator's Award, American Lung Association of California, $15,000. 7/1/91-6/30/92.

"Safety and Efficacy of Aerosolized Adenovirus Containing CFTR in Mammals." University of Pennsylvania — Cystic Fibrosis Foundation $100,000. 8/1/93-7/30/95.

"Gene Therapy for Cystic Fibrosis Lung Disease Using Second Generation Adenovirus." Project 3 University of Pennsylvania — NIDDK, $1,085,720. 9/30/94-9/29/99.

"A Randomized, Double-Blind Multicenter Study Evaluating the Effect of Montelukast Sodium to Salmeterol on the Inhibition of Exercise-Induced Bronchoconstriction." Merck & Co $32,688. 10/01/96-10/01/97.

Epidemiologic Study of Cystic Fibrosis" Genentech, Inc. $42,000.00. 11/01/94-11/01/98.

"A Phase IV Multicenter Randomized Trial in Patients with Cystic Fibrosis to Determine the Relative Efficacy of Pulmozyme Delivered by two Different Systems." Genetech, Inc. $8,500. 12/01/95-12/01/96.

"Long Term Safety Study of Zileuton Controlled-release Plus Usual Care Versus Placebo Plus Usual Care in Patients with Asthma." Abbott Laboratories. 3/18/97-3/18/98.

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APPENDIX B

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Abstracts

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A Novel A$_1$ Adenosine Receptor Antagonist (L-97-1) Reduces Pulmonary Inflammation in Allergic Rabbits

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Asthma is an airway disease characterized by bronchial hyperresponsiveness (BHR) and inflammation. In both humans and allergic rabbits, responses to allergen inhalation are characterized by BHR and airway inflammation. The effect of oral L-97-1, an adenosine A$_1$ receptor antagonist on bronchial inflammatory response to allergen inhalation was studied in a rabbit model of BHR following allergen inhalation. New Zealand White rabbits were made hyperresponsive (HR) to house dust mite (HDM) allergen and screened for BHR to histamine (HIST). Animals that attained a PC_{3x} (concentration of HIST required to produce a 30% reduction in lung dynamic compliance, C_{dyn}) of ≤ 10mg/ml were considered HR. In five control animals bronchoalveolar lavage (BAL) fluid was obtained from the rabbits at 0, 6 and 24 hrs time points following HDM inhalation (2500 AU). Two weeks later, the procedure was repeated on the same animals, following L-97-1 (1 mg/kg, oral) 1-hour prior to HDM allergen. BAL samples were obtained for total and differential cell counts. At 6 hrs, L-97-1 reduced total cells (control: 3.0±1.0x10^6 cells; L-97-1: 1.3±0.3x10^6), lymphocytes (control: 676±57 cells; L-97-1: 130±35), neutrophils (control: 1,90±0.20; L-97-1: 0.30±0.02) and eosinophils (control: 43077±313; L-97-1: 28772±189) (n= 5, p<0.05, ANOVA). The reduction in neutrophil cell count was sustained up to 24 hrs (control: 1.20±0.07 x10^6; L-97-1: 0.60±0.09x10^6) (n = 5,p<0.05, ANOVA). At 24 hours L-97-1 produced no significant differences in other cell types versus controls. L-97-1 inhibits bronchial inflammation following HDM allergen challenge in allergic rabbits.

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Pharmacological Characterization of CAT-213 an Anti-Eotaxin1 Neutralizing Antibody

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The potential therapeutic value of neutralising the effects of eotaxin1, an important regulator of eosinophil and mast cell function, in allergic disease such as asthma is under investigation with CAT-213, an anti-eotaxin1 IgG4. This work characterises the pharmacology of CAT-213, a human antibody produced using phage display technology. CAT-213 has high affinity (K_D 8.8pM) and specificity for eotaxin1 (no binding to MCP-1, -2, -3, -4 or eotaxin2, 3 by ELISA). CAT-213 inhibits the ability of eotaxin1 (3-10nM) to cause an increase in intracellular calcium levels and migration of human CCR3-expressing L1.2 cells, and evoke shape change and migration of human eosinophils in vitro (IC_{50} 5nM, 0.48nM, 0.71nM and 1.6nM, respectively). CAT-213 inhibits monkey eotaxin1 but is a poor inhibitor of mouse eotaxin1. In cynomolgus monkey (cyno.), intradermal injection of human and cyno. eotaxin1 (10μg) and IL-13 (15μg) caused recruitment of leukocytes to the dermis (cell counts performed on skin biopsy). Administration of CAT-213 (20 & 100mg/kg i.v. and 0.1mg i.d.) significantly inhibited eosinophil recruitment induced by human eotaxin (52%, 62% and 92% inhibition). CAT-213 (100mg/kg i.v.) significantly inhibited leukocyte chemotaxis caused by cyno. eotaxin and IL-13 (52% and 72% inhibition). CAT-213 is safe and well tolerated in monkey and man and has an elimination half-life of 8 days in man. Serum from healthy subjects injected with CAT-213 (5 & 10mg/kg single i.v. infusion) was able to inhibit eotaxin1 induced eosinophil shape change for up to 92 days.

In conclusion, CAT-213 can potently inhibit eotaxin1 and eosinophil function in vitro and in vivo and has a long duration of action. This pharmacological profile, taken together with the previously reported ability of CAT-213 to inhibit the eosinophil chemotactic activity of sputum from moderate and severe asthmatics, suggests that CAT-213 may provide control of airway eosinophilia in patients with asthma.

This Abstract is Funded by: CAT

Aminosterols, a Novel Class of Compounds, Inhibit Airway Hyperresponsiveness and BAL Eosinophilia in a Murine Asthma Model

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Aminosterols are a novel class of small molecules first identified as natural products in tissues of the dogfish shark, *Squalus acanthias*. We have previously identified a synthetic aminosterol molecule, MSI-1432, with potent activity in inhibiting airway hyperresponsiveness (AHR) and bronchial alveolar lavage (BAL) eosinophilia in a murine model of asthma. MSI-1432 is an ethylene diamine conjugate of methyl 3-oxo-6α-hydroxy-5α-cholan-24-oate. During characterization of the pharmacokinetic profile of MSI-1432, we found that MSI-1432 was completely converted to its carboxylic acid in vivo by esterases. We sought to determine whether the carboxylic acid of MSI-1432, MSI-1433, is the active component mediating the effect of MSI-1432 in inhibiting antigen-induced AHR and BAL eosinophilia. METHODS: B6D2F1/J mice were sensitized to *Aspergillus fumigatus* intranasally on days 0, 7, 14 and 15. Mice (6-10/group) were treated interperitoneally with either MSI-1432 (10 mg/kg), MSI-1433 (10 mg/kg), or vehicle daily. Approximately 12 hours after the last antigen administration, airway responsiveness was determined by serotonin-induced airway pressure time index methodology. BAL was collected to determine cellularity and differential counts. RESULTS: MSI-1433 markedly inhibited antigen-induced AHR and BAL eosinophilia. MSI-1433 treated mice had normal body weight gain and spleen weights whereas MSI-1432 caused weight loss likely due to peritoneal adhesion. CONCLUSION: Aminosterol MSI-1433 is as effective as MSI-1432 in inhibiting AHR and BAL inflammation with a better safety profile.

This Abstract is funded by: NIH grant 2R44 HL64531-02 and Genaera Corporation

Roflumilast, a Novel, Selective PDE4 Inhibitor, Shows Early Onset of Efficacy in Asthma

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RATIONALE Roflumilast is a novel, orally active, selective phosphodiesterase (PDE4) inhibitor in clinical development for the treatment of asthma and chronic obstructive pulmonary disease (COPD). *In vitro* and *in vivo* experiments have shown multi-pathway anti-inflammatory properties of roflumilast that may translate into continuous and sustained improvements in lung function of patients with asthma. METHODS In randomized, double-blind, multicenter studies, 702 patients with stable asthma received roflumilast 500 μg once daily for 12 weeks. Lung function was assessed daily by measuring peak expiratory flow (PEF) in the morning and was recorded by the patient. Change in morning PEF from baseline was analyzed from pooled data. RESULTS The mean baseline forced expiratory volume in 1 second (FEV_1) was 73% of predicted at randomization, mean morning PEF was 360 L/min and mean morning PEF at baseline was 77% of predicted. Statistically significant improvement in lung function was seen already after one day of treatment with roflumilast. Mean morning PEF increased by 13.2 ± 1.76 L/min (p=0.006) from baseline. After 14 days of treatment, mean morning PEF improved by 11.79 ± 1.96 L/min (p<0.0001) and continued to increase during the 12 weeks period. At the end of the roflumilast treatment, a clinically relevant mean improvement of 24.21 ± 2.58 L/min (p<0.0001) was attained. CONCLUSIONS In patients with asthma, early onset of efficacy of roflumilast occurred as early as one day following the start of treatment. Roflumilast continued to improve lung function throughout the 12 weeks of therapy and reached clinically relevant levels. Thus, the anti-inflammatory activity of roflumilast provides rapid onset of efficacy and steady, continuous improvement of lung function.

This Abstract is Funded by: ALTANA Pharma AG

Effects of Inhaled EPI-12323 on Allergen Response in Allergic Asthmatics

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Rationale: The aim of this clinical trial was to investigate whether repeated inhalation of EPI-12323, a nonglucocorticoid steroid, reduces the early-phase (EAR), late-phase (LAR) reactions and bronchial hyperresponsiveness after allergen challenge in patients with mild allergic asthma. Methods: The study was a DB, PC, R crossover trial. Patients underwent a Mch challenge, a dose-ascending allergen challenge and a single dose allergen challenge during the screening period. Patients were randomized to one of 2 treatment sequences (EPI/pbo, pbo/EPI). Each treatment period lasted for 5 days with a minimum 3 week washout between sequences. Patients received 25 mg EPI or pbo once daily with the Pari nebulizer. On days 4 and 6, patients had bronchial MCh hyperresponsiveness determined. On day 5, patients were subjected to a single dose allergen challenge. 22 asthmatic patients (mean FEV1 of 91% predicted) who experienced an EAR and LAR after allergen challenge (prescreened) participated in the study. Results: Treatment with placebo resulted in a mean maximal drop in FEV1 from hours 0-2 (EAR) of -30.6±14.7% (mean S.D.) and -21.1±10.8% fall in FEV1 3-8 hours (LAR). Following treatment with EPI-12323, there was a significant (P<0.05) attenuation in LAR compared to the corresponding placebo treatment arm; -14.6±12.7% vs -21.1±10.8%. The LAR AUC for FEV1 was also attenuated (-0.90±1.61 vs.-1.85±1.59 h.%, P<0.0[illegible]. There was a trend toward improvement in bronchial hyperresponsiveness following treatment with EPI-12323. There was no significant effect on EAR (-27.4±15.7% vs -30.5±14.7%). Conclusions: The study results suggest that once daily administration of EPI significantly attenuated the extent of LAR compared to placebo and reduced bronchial hyperresponsiveness in some patients. The magnitude of protection against allergen challenge is clinically relevant. EPI was well tolerated and no drug-related adverse events were reported.

This Abstract is Funded by: Epigenesis Pharmaceuticals

Effects of Proton Pump Inhibitor on Airway Hyperresponsiveness in Asthma with Gastroesophageal Reflux

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Study objectives: Previous data suggest the high incidence of gastroesophageal reflux (GER) in asthmatics, although the relationship between GER and the respiratory condition in asthmatics remain unclear. We investigated the incidence of GER in asthmatics and the association between the effects of proton-pump inhibitor (PPI) on respiratory functions and esophageal pH in asthmatics with GER.

Patients and Methods: Two hundreds ninety outpatients who attended our unit with asthma received GER symptoms questionnaire used at Mayo Clinic. Twenty-three of them who answered to have any GER symptom were treated with PPI (lansoprazole 30mg/day) for eight weeks, and investigated changes in the GER symptoms and peak expiratory flow rates (PEFR) before and after treatment. Furthermore, in six of twenty-three, airway hyperresponsiveness to methacholine and the esophageal pH for 24 hours were measured in order to evaluate the association between esophageal pH and the effect of PPI on GER during the test. Furthermore, the serum level of theophylline was analyzed in five patients for assessment of the PPI effect on theophylline metabolism.

Results: 139 of 254 asthmatics had answered to have any GER symptom including cough. Most of GER symptoms had improved except for cough after treatment with PPI. The airway hyperresponsiveness significantly improved after treatment with PPI (n=6, p<0.03), although PEF and FEV1 were not significantly changed.

Conclusion: These results suggest that PPI may be an effective drug for asthmatics with GER through suppression of airway hyperresponsiveness.

This Abstract is Funded by: None

Effects of Inhaled EPI-12323 on Allergen Response in Allergic Asthmatics

F. Kanniess[1], J. Bäfer[2], J. Kleine-Tebbe[3], H. Magnussen[1]. [1]Pulmonary Research Institute, Grosshansdorf, Germany; [2]University Hospital Mainz, Mainz, Germany; [3]Humboldt University, Berlin, Germany.

Rationale: The aim of this clinical trial was to investigate whether repeated inhalation of EPI-12323, a nonglucocorticoid steroid, reduces the early-phase (EAR), late-phase (LAR) reactions and bronchial hyperresponsiveness after allergen challenge in patients with mild allergic asthma. Methods: The study was a DB, PC, R crossover trial. Patients underwent a Mch challenge, a dose-ascending allergen challenge and a single dose allergen challenge during the screening period. Patients were randomized to one of 2 treatment sequences (EPI/pbo, pbo/EPI). Each treatment period lasted for 5 days with a minimum 3 week washout between sequences. Patients received 25 mg EPI or pbo once daily with the Pari nebulizer. On days 4 and 6, patients had bronchial MCh hyperresponsiveness determined. On day 5, patients were subjected to a single dose allergen challenge. 22 asthmatic patients (mean FEV1 of 91% predicted) who experienced an EAR and LAR after allergen challenge (prescreened) participated in the study. Results: Treatment with placebo resulted in a mean maximal drop in FEV1 from hours 0-2 (EAR) of -30.6±14.7% (mean S.D.) and -21.1±10.8% fall in FEV1 3-8 hours (LAR). Following treatment with EPI-12323, there was a significant ($P<0.05$) attenuation in LAR compared to the corresponding placebo treatment arm: -14.6±12.7% vs -21.1±10.8%. The LAR AUC for FEV1 was also attenuated (-0.90±1.61 vs.-1.85±1.59 h.%, $P<0.0$). There was a trend toward improvement in bronchial hyperresponsiveness following treatment with EPI-12323. There was no significant effect on EAR (-27.4±15.7% vs -30.5±14.7%). Conclusions: The study results suggest that once daily administration of EPI significantly attenuated the extent of LAR compared to placebo and reduced bronchial hyperresponsiveness in some patients. The magnitude of protection against allergen challenge is clinically relevant. EPI was well tolerated and no drug-related adverse events were reported.

This Abstract is Funded by: Epigenesis Pharmaceuticals